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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
RAWLINGS, STEPHEN L	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 11/02/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/619,310	THASTRUP ET AL.	
	Examiner	Art Unit	
	Stephen L. Rawlings, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 1 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *21 July 2004*.

2a)☐ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-41* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) _____ is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☒ Claim(s) *1-41* are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☒ Other: *Notice to Comply*.

DETAILED ACTION

1. The reply filed July 21, 2004 is acknowledged and has been entered.

2. The restriction and election requirement set forth in the Office action mailed November 4, 2003 is withdrawn in favor of the new restriction and election requirement set forth below.

3. Applicant's arguments traversing the restriction and election requirement set forth in the Office action mailed November 4, 2003 have been carefully considered but are moot in view of the new restriction and election requirement set forth below.

4. Claims 1-41 are pending in the application and are currently subject to restriction.

Deficient Compliance with Sequence Rules

5. This application contains sequence disclosures that are encompassed by the definitions for nucleotide and/or amino acid sequences set forth in 37 C.F.R. § 1.821(a)(1) and (a)(2). However, this application fails to comply with the requirements of 37 C.F.R. §§ 1.821-1.825 for the reason(s) set forth on the attached Notice To Comply With Requirements For Patent Applications Containing Nucleotide Sequence And/Or Amino Acid Sequence Disclosures.

As noted on the attached Notice to Comply, the paper copy of the Sequence Listing and the computer-readable form (CFR) are not the same, since, for example, the sequence listed as SEQ ID NO: 4 differs.

Appropriate action correcting this deficiency is required.

Election/Restrictions

6. Restriction to one of the following inventions is required under 35 U.S.C. 121:

Group I. Claims 7 and 38, drawn to a fluorescent protein having the amino acid sequence depicted in Figure 3 (SEQ ID NO: 18), classified in class 530, subclass 350.

Group II. Claims 7 and 39, drawn to a fluorescent protein having the amino acid sequence depicted in Figure 4 (SEQ ID NO: 20), classified in class 530, subclass 350.

Group III. Claims 7 and 40, drawn to a fluorescent protein having the amino acid sequence depicted in Figure 5 (SEQ ID NO: 22), classified in class 530, subclass 350.

Group IV. Claim 11, drawn to a nucleotide sequence encoding a fluorescent protein having the amino acid sequence depicted in Figure 3 (SEQ ID NO: 18), classified in class 536, subclass 23.5.

Group V. Claim 11, drawn to a nucleotide sequence encoding a fluorescent protein having the amino acid sequence depicted in Figure 4 (SEQ ID NO: 20), classified in class 536, subclass 23.5.

Group VI. Claim 11, drawn to a nucleotide sequence encoding a fluorescent protein having the amino acid sequence depicted in Figure 5 (SEQ ID NO: 22), classified in class 536, subclass 23.5.

Group VII. Claim 18, drawn to a method for measuring protein kinase activity, classified in class 435, subclass 15.

Group VIII. Claim 18, drawn to a method for measuring phosphatase activity, classified in class 435, subclass 21.

Group IX. Claim 19, drawn to a method for measuring metabolic activity, classified in class 435, subclass 7.2.

Group X. Claims 20, 21, and 34-37, drawn to a method for monitoring or detecting the expression of one or more genes in a living cell by measuring fluorescence of a protein or proteins encoded by the genes, classified in class 435, subclass 15.

Group XI. Claim 22, drawn to a method for visualizing organelle or cell processes in living cells, classified in class 424, subclass 9.6.

6. Claims 1-6, 8-10, 12-17, 23-33, and 41 are linking claims. The restriction requirement among the linked inventions is subject to the nonallowance of the linking claim(s). Upon the allowance of the linking claim(s), the restriction requirement as to the linked inventions shall be withdrawn and any claim depending from or otherwise including all the limitations of the allowable linking claims will be entitled to examination in the instant application. Applicants are advised that if any such claims depending from or including all the limitations of the allowable linking claims are presented in a continuation or divisional application, the claims of the continuation or divisional application may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Where a restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. *In re Ziegler*, 44 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

7. The inventions are distinct, each from the other because of the following reasons:

The inventions of Groups I-VI are patentably distinct products.

The claims of Groups I-III are drawn to patentably distinct proteins, each having a unique amino acid sequence that differs from that of the others. Group I is a protein comprising the amino acid sequence of SEQ ID NO: 16 but for substitution of the amino acid sequence at positions 64-67 by lys-ser-his-gly (i.e., SEQ ID NO: 18). In contrast, Group II is a protein comprising the amino acid sequence of SEQ ID NO: 16 but for substitution of the amino acid sequence at positions 64-67 by lys-ser-tyr-gly (i.e., SEQ ID NO: 20), whereas Group III is a protein comprising the amino acid sequence of SEQ ID NO: 16 but for substitution of the amino acid sequence at positions 64-67 by lys-thr-tyr-gly (i.e., SEQ ID NO: 22).

It is recognized that the inventions of Groups I-III are different analogues of a naturally occurring green fluorescent protein (GFP), which have been produced by altering the amino acid residues of the chromophore, or adjacent to the chromophore, of the naturally occurring molecule. Because the structure and nature of the amino acid residues of the chromophore and its proximate amino acid residues varies in the different analogues, and because it is these residues that confer the ability of the proteins to fluoresce, the different analogues do not share a common structural feature that correlates with their common ability to fluoresce.

Because the inventions of Groups I-III are proteins having unique amino acid sequences, and because the different proteins do not share a common structural feature that correlates with their common ability to fluoresce, the search required to examine any one of the groups is not the same, nor is it coextensive with the search required to examine any other. Therefore, a different search would have to be performed to examine claims drawn to any one of the inventions of Groups I-III. Having to perform more than one search would unduly burden the Examiner; therefore, according to MPEP § 803, since the inventions are distinct, each from the other, and the claims drawn to these inventions cannot be searched and examined together without serious burden, the restriction of Groups I-III is proper. See MPEP § 809.

The claims of Groups IV-VI are drawn to patentably distinct nucleic acids, each having a unique polynucleotide sequence that differs from that of the others and encoding a different protein having a distinct amino acid sequence. Group IV is a nucleic acid encoding a protein comprising the amino acid sequence of SEQ ID NO: 16 but for substitution of the amino acid sequence at positions 64-67 by lys-ser-his-gly (i.e., SEQ ID NO: 18). In contrast, Group V is a nucleic acid encoding a protein comprising the amino acid sequence of SEQ ID NO: 16 but for substitution of the amino acid sequence at positions 64-67 by lys-ser-tyr-gly (i.e., SEQ ID NO: 20), whereas Group VI is a nucleic acid encoding a protein comprising the amino acid sequence of SEQ ID NO: 16 but for substitution of the amino acid sequence at positions 64-67 by lys-thr-tyr-gly (i.e., SEQ ID NO: 22).

It is recognized that the inventions of Groups IV-VI encode different analogues of a naturally occurring green fluorescent protein (GFP), which have been produced by altering polynucleotide sequence encoding the amino acid residues of the chromophore, or adjacent to the chromophore, of the naturally occurring molecule. Because the structure and nature of the amino

acid residues of the chromophore and its proximate amino acid residues varies in the different analogues, and because it is these residues that confer the ability of the proteins to fluoresce, the different analogues do not share a common structural feature that correlates with their common ability to fluoresce.

Because the inventions of Groups IV-VI are distinct nucleic acid molecules encoding different proteins having unique amino acid sequences, and because these different proteins do not share a common structural feature that correlates with their common ability to fluoresce, the search required to examine any one of the groups is not the same, nor is it coextensive with the search required to examine any other. Therefore, a different search would have to be performed to examine claims drawn to any one of the inventions of Groups IV-VI. Having to perform more than one search would unduly burden the Examiner; therefore, according to MPEP § 803, since the inventions are distinct, each from the other, and the claims drawn to these inventions cannot be searched and examined together without serious burden, the restriction of Groups IV-VI is proper. See MPEP § 809.

The inventions of any one of Groups I-III and any one of Groups IV-VI are patentably distinct, each from the other, because the inventions of Groups I-III are polypeptides, whereas the inventions of Groups IV-VI are nucleic acids. Polypeptides and polynucleotides are chemically distinct products, since polypeptides are composed of polymers of amino acids, whereas polynucleotides are composed of polymers of nucleotides. Any relationship between a polynucleotide and a polypeptide is dependent upon the information provided by the nucleotide sequence of the polynucleotide, as it corresponds to an "open reading frame" encoding the amino acid sequence of the polypeptide. However, the nucleic acid of Group IV does not encode the polypeptide of either Group II or III; the nucleic acid of Group V does not encode the polypeptide of either Group I or III; and the nucleic acid of Group VI does not encode the polypeptide of either Group I or II. Furthermore, a polypeptide can be produced by means, other than the recombinant means by which a polynucleotide encoding a polypeptide might be used to produce the polypeptide, since a polypeptide can be produced (or isolated) by biochemical means, including, for example, affinity chromatography. In addition, while the polynucleotide might encode the polypeptide, generally, it can also encode another polypeptide using the information provided by an alternative open reading frame; and furthermore, since a

polynucleotide can be used as a probe in hybridization-based analyses, the information provided by a polynucleotide can be used isolate different polynucleotides encoding polypeptides, which have amino acid sequences that differ from the amino acid sequence encoded by the disclosed polynucleotide. Consequently, the disclosed relationship between a polynucleotide capable of encoding a polypeptide and the polypeptide is not exclusive, since either the claimed polynucleotide or the claimed polypeptide can also be related to other polynucleotides or polypeptides, which are materially and chemically different from the claimed inventions. Therefore, the inventions of any one of Groups I-III and any one of Groups IV-VI are patentably distinct products.

The inventions of Groups I-III and the inventions of Groups IV-VI have acquired a separate status in the art, as evidenced by their different classifications, and the search performed in examining claims drawn to a polynucleotide is a different from the search performed in examining claims drawn to a polypeptide. Apart from the searching patent databases using the patent classification of the claimed subject matter, a thorough search of the technical literature is particularly pertinent, and since such a search is performed by a series of key word queries of relevant databases, each search would be performed using a different set or series of key words. Therefore, the search and considerations necessary in examining the merit of claims of any one of Groups I-III would not suffice to provide adequate information regarding the merit of the claims of any one of Groups IV-VI, and vice versa, since the searches are not the same, nor are they one coextensive in scope and nature. Because different searches would have to be performed to examine the inventions of any one of Groups I-III and any one of Groups IV-VI, an examination of both would constitute a serious burden. Moreover, because the disclosed relationship between the polynucleotide and the polypeptide encoded by the polynucleotide is not absolute or exclusive of other relationships with different polynucleotides or polypeptides, the search of either group will likely provide information that is relevant to one but not the other; and as such, searching one in addition to the other would be unduly burdensome.

Since the inventions of any one of Groups I-III and any one of Groups IV-VI are patentably distinct from the other and because the examination of both could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

The inventions of Groups VII-XI are, or have been interpreted as patentably distinct methods.

The inventions of Groups VII and VIII are patentably distinct, each from the other, because the invention of Group VII is a method for measuring protein kinase activity, whereas the invention of Group VIII is a method for measuring phosphatase activity. The inventions have acquired a different status in the art, as evidenced by their different classification; moreover, the inventions are different process necessarily comprising different steps measuring different end-points by different means, since the invention of Group VII measures kinase activity and the invention of Group VIII measures phosphatase activity.

Because the inventions are different processes, the search required to examine the invention of Group VII is not the same, nor is it coextensive with the search required to examine claims drawn to the invention of Group VIII. Because the same search would not suffice to examine claims drawn to both inventions, each invention requires that a different search be performed. Having to search claims drawn to both inventions would thus require more than one search to be performed, which would be unduly burdensome.

Since the inventions of Groups VII and VIII are patentably distinct from the other and because the examination of both could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

The invention of Group IX is patentably distinct from the inventions of Groups VII and VIII, because the inventions are materially different processes for measuring a metabolic activity, since the invention of Group IX measures the metabolic activity *in vivo*, whereas the invention of Groups VII and VIII measure the metabolic activity *in vitro*. Thus, the invention of Group IX is a process that uses an intact, living cell, whereas the inventions of Groups VII and VIII are processes that uses cell extracts comprising fluorescent proteins or purified fluorescent proteins. Furthermore, the inventions have acquired a different status in the art, as evidenced by their different classification.

Because the inventions are different processes, the search required to examine the invention of Group IX is not the same, nor is it coextensive with the search required to examine claims drawn to the inventions of either of Groups VII or VIII. Because the same search would not suffice to examine claims drawn to both inventions, each invention requires that a different

search be performed. Having to search claims drawn to both inventions would thus require more than one search to be performed, which would be unduly burdensome.

Since each of the inventions of Groups VII-IX is patentably distinct from the others and because the examination of more than any one could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

The inventions of Group X and the inventions of any one of the Groups VII-IX are patentably distinct, each from the other, because the inventions are materially different methods, comprise different process steps, and have different purposes. The inventions of Group X are methods for monitoring or detecting the expression of one or more genes, whereas the inventions of Groups VII-IX are methods for measuring metabolic activity. The inventions of Group X minimally comprise measuring fluorescence produced by a living cell. In contrast, the inventions of Groups VII-IX minimally comprise measuring, for example, enzymatic processes, such as phosphorylation and dephosphorylation. Consequently, the inventions have acquired a different status in the art, as evidenced by their different classification.

Because the inventions are different processes, the search required to examine the invention of Group X is not the same, nor is it coextensive with the search required to examine claims drawn to the inventions of any one of Groups VII-XI. Because the same search would not suffice to examine claims drawn to both inventions, each invention requires that a different search be performed. Having to search claims drawn to both inventions would thus require more than one search to be performed, which would be unduly burdensome.

Since each of the inventions of Groups VII-X is patentably distinct from the others and because the examination of more than any one could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

The inventions of Group XI and the inventions of any one of the Groups VII-X are patentably distinct, each from the other, because the inventions are materially different methods, comprise different process steps, and have different purposes. The inventions of Group XI are methods for visualizing organelle or cell processes in living cells, whereas the inventions of Group X are methods for monitoring or detecting the expression of one or more genes and the inventions of Groups VII-IX are methods for measuring metabolic activity. The inventions of Group X minimally comprise visualizing fluorescence produced by a living cell using, for

example, a microscope. In contrast, the inventions of Group X minimally comprise measuring fluorescence produced by a living cell and the inventions of Groups VII-IX minimally comprise measuring, for example, enzymatic processes, such as phosphorylation and dephosphorylation. Consequently, the inventions have acquired a different status in the art, as evidenced by their different classification.

Because the inventions are different processes, the search required to examine the invention of Group XI is not the same, nor is it coextensive with the search required to examine claims drawn to the inventions of any one of Groups VII-X. Because the same search would not suffice to examine claims drawn to both inventions, each invention requires that a different search be performed. Having to search claims drawn to both inventions would thus require more than one search to be performed, which would be unduly burdensome.

Since each of the inventions of Groups VII-XI is patentably distinct from the others and because the examination of more than any one could not be made without serious burden, it is proper to restrict one from the other. See MPEP § 803.

Inventions in Groups I-III and inventions in Groups VII, VIII, X, and XI are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product as claimed, namely a protein can be used in a materially different process of using that product, such as the process of using the protein as an immunogen to produce an antibody that binds the protein.

Inventions in Groups IV-VI and inventions in Groups IX and X are related as product and process of use. The inventions can be shown to be distinct if either or both of the following can be shown: (1) the process for using the product as claimed can be practiced with another materially different product or (2) the product as claimed can be used in a materially different process of using that product (MPEP § 806.05(h)). In the instant case, the product as claimed, namely a nucleic acid or a host cell comprising a nucleic acid can be used in a materially different process of using that product, such as the process of producing a protein encoded by the nucleic acid.

The inventions of Group I-III and the inventions of Group IX are unrelated because the products of Group I-III are not specifically used or otherwise involved in the processes of Group IX.

The inventions of Group IV-VI and the inventions of Groups VII, VIII, and XI are unrelated because the products of Group IV-VI are not specifically used or otherwise involved in the processes of Groups VII, VIII, and XI.

8. Because these inventions are distinct for the reasons given above and also because the search required for any one group is not required for any other group and/or the inventions have acquired a separate status in the art as shown by their different classification or their recognized divergent subject matter, searching more than one invention encompassed by the claim would constitute a serious burden; therefore, restriction for examination purposes as indicated is proper.

9. Applicant is advised that the reply to this requirement to be complete must include an election of the invention to be examined even though the requirement be traversed (37 CFR 1.143).

10. The examiner has required restriction between product and process claims. Where applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims that depend from or otherwise include all the limitations of the allowable product claim will be rejoined in accordance with the provisions of MPEP § 821.04. **Process claims that depend from or otherwise include all the limitations of the patentable product** will be entered as a matter of right if the amendment is presented prior to final rejection or allowance, whichever is earlier. Amendments submitted after final rejection are governed by 37 CFR 1.116; amendments submitted after allowance are governed by 37 CFR 1.312.

In the event of rejoinder, the requirement for restriction between the product claims and the rejoined process claims will be withdrawn, and the rejoined process claims will be fully examined for patentability in accordance with 37 CFR 1.104. Thus, to be allowable, the rejoined

claims must meet all criteria for patentability including the requirements of 35 U.S.C. 101, 102, 103, and 112. Until an elected product claim is found allowable, an otherwise proper restriction requirement between product claims and process claims may be maintained. Withdrawn process claims that are not commensurate in scope with an allowed product claim will not be rejoined. See "Guidance on Treatment of Product and Process Claims in light of *In re Ochiai, In re Brouwer* and 35 U.S.C. § 103(b)," 1184 O.G. 86 (March 26, 1996). Additionally, in order to retain the right to rejoinder in accordance with the above policy, Applicant is advised that the process claims should be amended during prosecution either to maintain dependency on the product claims or to otherwise include the limitations of the product claims. **Failure to do so may result in a loss of the right to rejoinder.**

Further, note that the prohibition against double patenting rejections of 35 U.S.C. 121 does not apply where the restriction requirement is withdrawn by the examiner before the patent issues. See MPEP § 804.01.

11. Applicant is reminded that upon the cancellation of claims to a non-elected invention, the inventorship must be amended in compliance with 37 CFR 1.48(b) if one or more of the currently named inventors is no longer an inventor of at least one claim remaining in the application. Any amendment of inventorship must be accompanied by a request under 37 CFR 1.48(b) and by the fee required under 37 CFR 1.17(i).

Conclusion

12. Any inquiry concerning this communication or earlier communications from the examiner should be directed to Stephen L. Rawlings, Ph.D. whose telephone number is (571) 272-0836. The examiner can normally be reached on Monday-Friday, 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on (571) 272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Stephen L. Rawlings, Ph.D.
Examiner
Art Unit 1642

slr
October 27, 2004